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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,780	08/30/2001	Kevin P. Baker	P2548P1C10	2570

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,780	BAKER ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-26 and 35-36 are cancelled.

2. Claims 27-34 are pending and under examination.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

Objections/Rejections Withdrawn

4. The objection to the specification for not containing the updated status of USSNs 09/216,021, 09/218,517 and 09/254,311 is withdrawn in view of the amendments to the specification.

Response to Arguments

5. The rejection of claims 27-34 under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well-established utility is maintained.

The response submits that PRO357 polypeptides are useful as a diagnostic marker because PRO357 is encoded by a nucleic acid that is amplified in lung and colon tumors. Applicant states that the specification at page 137 discloses that the gene encoding the PRO357 polypeptide showed significant amplification, ranging from 2-fold to more than 8-fold in 40 different lung and colon primary tumors and tumor cell lines. Applicant maintains that ample evidence has been submitted (i.e., art of Orntoft et al, Hyman et al, Pollack et al, Bermont et al, Varis et al, and Hu et al and the

declarations of Audrey Goddard, Ph.D and Avi Askenazi, Ph. D) to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. Thus, the asserted utility is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. The art discloses that such correlations cannot be presumed. Regarding the correlation between genomic DNA amplification and increased mRNA expression, Pennica et al. (1998, PNAS USA 95:14717-14722, of record), who disclose that:

> "An analysis of WISP-, gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISPQ DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column, pp. 14720-14721, "Amplification and' Aberrant Expression of WISPS in Human Colon Tumors." See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Even if increased mRNA levels could be established for PRO357, it does not follow that polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung

adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 31 1-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, most are attributable to disease-independent differences between the samples (emphasis added, 2003, Nature Biotechnology 21:976-977). Additionally, Hanna J. S. et al (Pathology Associates Medical Laboratories, 1999) show that gene amplification does not reliably correlate with polypeptide over-expression, and thus, the level of polypeptide expression must be tested empirically. The art also shows that transcript levels do not correlate with polypeptide levels in normal tissues. See Haynes et al.

(1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances, which varied more than K-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 polypeptides. They concluded that

> the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 3o-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient"

(See Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291 , abstract).

Therefore, data pertaining to PRO357 genomic DNA do not indicate anything significant regarding the claimed PRO357 polypeptides. The data do not support the

specification's assertion that PRO357 polypeptides can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO357 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO357 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO357 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

At page 7 of the response, Applicant argues that to make a prima facie case of overcoming Applicants asserted utility, the PTO must establish that more likely than not, one of ordinary skill in the art would doubt the truth of Applicant's assertion that the claimed polypeptides have utility as a diagnostic. The response states that the claimed polypeptide is supported by a specific substantial and credible utility. This has been fully considered, but is not found persuasive. The rejection does not question the presumption of truth, or credibility of the asserted utility. The asserted utility as a cancer

diagnostic for the claimed PRO357 polypeptide is credible and specific, however, the asserted utility is not substantial. The data set forth in the specification are preliminary at best.

The response argues that Orntoft, Hyman et al and Pollack et al teach that in general, gene amplification increased mRNA expression. Applicant points to the declaration of Dr. Polakis, submitted under 37 C.F.R. 1.132 with the response filed 07 July 2004. Appellant characterizes the declaration as setting forth Dr. Polakis experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Applicant concludes that all of the submitted evidence supports Applicant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. In assessing the weight to be given to expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d

1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO357 (i.e., data regarding amplification of PRO357 genomic DNA), and does not disclose any information regarding PRO357 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al, Konopka et al, Chen et al (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al, LaBaer, Hanna et al, Haynes et al, Gygi et al, Lian et al, and Fessler et al, (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so the examiner could not independently evaluate them.

At the bottom of page 9 of the response, Applicant notes that the sale of gene expression chips to measure mRNA levels is a highly successful business. Applicant asserts that the research community believes that the information obtained from these

chips is useful, i.e., that it is more likely than not informative of the protein level. This has been fully considered but is not found persuasive. Evidence of financial success is not relevant to utility or enablement. Also, the chips may provide useful information about genes, but not polypeptides. Further, the success of gene chips and their focus is due to the in large part to the more copious and technically easier mRNA experiments as evidenced by Greenbaum (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8). Specifically, Greenbaum cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments

that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Further, those skilled in the art utilizing microarrays acknowledge that they reveal very little about the encoded protein. For example, Winstead states "For all the information gene microarrays provide, they reveal relatively little about proteins, the molecules that carry out most of the functions of a cell. Gene arrays detect the presence of messenger RNA, the chemical involved in translating DNA into protein. Tracking this middle step in the production process reveals nothing about three areas of interest to researchers: protein function, the abundance of protein in a cell, and modifications to proteins after they are produced – changes that may be critical in the development of disease." (top of pg. 3) (Winstead E. R., Genome News Network, "The Evolving Art of Arrays", www.genomenewsnetwork.org, pp. 1-4, 15 September 2000). Irving et al (Nature Biotechnology 18:932-933, September 2000) state: "But despite their obvious value in gene expression profiling, such arrays reveal relatively little information about the final concentrations of gene products in a cell, and they reveal nothing about post-translational modifications, protein activity, and protein-protein interactions (pg. 932, top left column). In view of the totality of evidence, the skilled artisan would not reasonably presume that PRO357 polypeptide is more highly expressed in normal kidney than kidney tumor based on the disclosure regarding "more highly expressed" PRO357 mRNA without actually testing for PRO357 polypeptide expression. The requirement for

such testing indicates that the asserted utility is not substantial, i.e., it requires further research to identify or confirm a "real world" use. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

At page 11 of the response, Applicant argues that the Ashkenazi declaration and the Hanna et al reference provide evidence that, even if gene amplification were not to result in overexpression of the encoded polypeptide, analysis of the expression of the polypeptide is useful in determining the course of treatment. Applicant argues that the examiner is incorrect in asserting that such testing involves further characterization of the PRO357 polypeptide itself. Applicant argues that such testing is for the purpose of characterizing the tumors into medically relevant categories. Applicant adds that such testing techniques were routine in the art of clinical oncology at the time of filing of the instant application. This has been fully considered but is not found to be persuasive. First, testing whether or not a polypeptide is overexpressed in a particular tumor yields information regarding the tumor and the polypeptide itself. Second, the specification does not assert that PRO357 polypeptide is useful as a tumor categorization agent. Such is only presented in the arguments and declaration. Third, even if such were asserted in the specification as filed, the skilled artisan would still have to perform further research to reasonably confirm whether or not PRO357 polypeptide is overexpressed in any tumor, since the expression levels of PRO357 polypeptide are not disclosed in the specification. The requirement for such further

research indicates that the utility is not in currently available form, i.e., it is not substantial. Finally, it is no small matter to go from information regarding protein expression levels in a tumor to designing a therapeutic regimen specific to the protein expression profile. In Hanna et al., Herceptin was discussed as a drug specific to tumors expressing HER-2/neu. Herceptin had been known prior to the publication of Hanna et al. No such drug is disclosed in the specification, nor in the prior art, regarding the PRO357 polypeptide. Identifying a drug specific for PRO341 would involve more than routine experimentation, as it would require a great amount of experimentation (e.g., screening agents for effects on PRO357 polypeptide and on tumor), considering there is no guidance or working examples relative to such drugs in the specification or the prior art.

For these reasons the rejection is maintained.

6. The rejection of claims 27-34 rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention is maintained.

7. The rejection of claims 27-34 under 35 U.S.C. 112, first paragraph, because the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The response field 10/20/2005 argues that based on the data provided in Example 28 of the present specification and as addressed in response to the utility rejection, one of ordinary skill in the art would be enabled to use the claimed polypeptides at least as diagnostic markers because it is generally accepted in the art that gene amplification correlates with protein overexpression. Applicant reviews the factors for determining whether undue experimentation is required, i.e., *In re Wands*. In response to these arguments and as addressed above the literature reports that gene amplification does not correlate with increased mRNA levels (see Pennica et al and Konopka et al) and increased mRNA levels do not correlate with increased polypeptide levels in healthy tissue (see Haynes et al, Gygi et al, Lian et al, Fessler et al) or cancerous tissue (see Haynes et al, LaBaer, Chen et al, Hanna et and Greenbaum et al, Winstead and Irving et al). Thus, the state of the prior art underscores the unpredictability in the art and the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels gene amplification or mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. The specification does not disclose PRO357 polypeptide expression in any cancerous tissue compared to a matched tissue control, the specification does not quantitate PRO357 in cancerous tissue compared to a matched tissue control, there is no guidance or direction provided pertaining to the significance of PRO357 expression in cancer and the specification does not disclose any function or biological activity of PRO357.

Thus, in view of the lack of guidance, lack of examples, and lack of predictability in the art as evidenced from the above references, one skilled in the art would be forced into undue experimentation in order to practice the claimed invention and the rejection is maintained.

8. The rejection of claims 27-34 under 35 U.S.C. 102(b) as being anticipated by Botstein et al (WO 99/35170, 7/15/1999) is maintained.

The response filed 10/20/2005 amends the priority claim of the present application and argues that the instant claims have an effective filing date of at least 12/22/1998, which is prior to the publication date of the applied reference. In response to this argument, and as set forth above, the present claims are not supported by a substantial or well-established utility and lack enablement under the first paragraph of 35 U.S.C. 112. Again, Applicant is reminded that benefit to a prior-filed application requires written description and enablement under the first paragraph of 35 U.S.C. 112. Therefore, the rejection is maintained for reasons already of record.

Conclusion

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER